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Formulation and evaluation of Labetalol mouth dissolving tablets

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Abstract

The objective of the present work was to formulate mouth dissolving tablet enriched with taste masking agent to provide rapid onset of action of Labetalol increasing its therapeutic efficacy and also increase the compliance amongst geriatric, pediatric and uncooperative patients. Total seven formulations of MDTs were prepared using direct compression (LODT1 to LODT4) and sublimation method (LODT5 to LODT7). The concentration of the super-disintegrant or the sublimating agent was varied depending on the method. Mannitol/Lactose was used as the binder as well as sweetener while saccharin sodium was used as the additional taste masking agent in the formulations. All the formulations were subjected to post compression evaluation test and the results indicate that the formulation had hardness of 3 Kg/cm^2, thickness of 3 mm, weight variation in the range of 2.7-3.3 %, friability of less than 1 %, drug content in the range of 97.2 to 98.9 %, wetting time from 17 to 49 seconds with water absorption ratio of more than 75 %, disintegration time of less than 30 seconds and a drug release of more than 80 % over a period of 5 minutes. The formulations were found to be stable under accelerated conditions for a period of 3 months with almost negligible change in the critical parameters.

Keywords: Labetalol, hypertension, mannitol, lactose, mouth dissolving, tablet

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Introduction

Amongst the dosage forms administered via the oral route solid dosage forms like tablet and capsules are quite popular and preferred dosage forms due to ease of production, ease of marketing, dosing accuracy, and physical and chemical stability (Dev and Maity, 2010. A delivery system based on bucaal delivery offers an excellent approach to delivery of proteins and peptides by releasing drugs at a preset rate in the oral cavity and its absorption through the oral mucosa (Chein, 1992). The oral dissolving tablets are intended for the delivery of drugs like steroids and analgesics that have very low bioavailability through the GI tract (Mccarty, 1991).[3]

Labetalol hydrochloride is a selective α_1- and non selective β- adrenoceptor blocker usually indicated for the treatment of hypertension (drugbank, 2020). It is used parenterally for immediately reducing blood pressure in case of severe hypertension or in hypertensive crisis for the regulation of blood pressure in patients suffering with pheochromocytoma, and also for producing controlled hypotension during anesthesia in order to reduce bleeding that result from surgical procedures. The drug is characterized by a very high first pass hepatic metabolism being found that 18% of the orally administered drug undergoes first pass metabolism. The drug is bound to plasma proteins (50%) and has a half life of 4.9 h.

The peak plasma levels of labetalol are reported to be achieved after 1-2 hours post oral administration and this presents a therapeutic challenge for obtaining relief from the symptoms of the hypertensive crisis.

A few reports of mouth dissolving tablets (MDTs) of Labetalol have been found in literature (Shahidullah and Jeelani, 2019a, 2019b; Rebecca et al., 2016, Gottumukkala et al., 2014). The aim of the present work is to formulate and perform the evaluation of mouth dissolving tablets of Labetalol hydrochloride.

Material and Methods

Labetalol hydrochloride was obtained as a generous gift sample from IPCA Pharmaceuticals. Crospovidone, Mannitol, Microcrystalline cellulose and other additives were procured from various suppliers and used as obtained.

Preformulation Studies

The procured sample of labetalol hydrochloride was observed for its appearance, color and taste in order to characterize the physical parameters. Melting point of the sample was determined by open capillary method. In order to check the solubility qualitative method was used.

Calibration curve of Labetalol in phosphate buffer pH 6.8 solution

Accurately weighed 50 mg of Labetalol was taken in 50 mL volumetric flask and dissolved in 3 mL methanol and volume was made up with PBS pH 6.8 to the mark resulting in 1000 µg/mL stock solution. From the above stock solution 10 mL was taken in another 100 mL volumetric and volume was made up

with PBS pH 6.8 to mark and the concentration of solution become 100 µg/mL. After that from the above solution the aliquots of 1-10 mL of stock solution were taken into a series of 10 mL volumetric flask and volume was made up to the mark with PBS pH 6.8 and it was analyzed at λ max 285nm using UV

Preparation of MDTs of Labetalol

Direct Compression method (Subramanyam, 2001)

The MDTs of labetalol were prepared by direct compression method according the batch formula given in Table 1.

All the ingredients were separately sifted through 60 mesh sieve. The drug and microcrystalline cellulose were mixed in small portions of both and blending it to get a uniform mixture. This mixture was kept aside for blending. All the other ingredients were accurately weighed and mixed in geometrical order and tablets and blended in a polybag. The blend was compressed to tablets of 8 mm sizes using flat round punch using tablet compression machine.

Table 1 Batch formula per tablet using direct compression method

Ingredient (mg)	Formulation code			
	LODT1	LODT2	LODT3	LODT4
Labetalol	5	5	5	5
Sodium starch glycolate	7	14	21	28
Saccharin Sodium	12	12	12	12
D-mannitol	114	107	100	93
Microcrystalline Cellulose	54	54	54	54
Methyl cellulose	3	3	3	3
Talc	3	3	3	3
Magnesium stearate	2	2	2	2
TOTAL	**200**	**200**	**200**	**200**

Sublimation method (Aly et al., 2005)

Sublimation method has been used occasionally for the formulation of MDTs. As no reported sublimation method using camphor was found in literature for formulation of labetalol MDTs, we formulated three formulations using varying concentration of camphor as the sublimating agent. The composition of the formulation developed is presented in Table 2

Accurately weighed ingredients were sifted through sieve no.44 and thoroughly mixed for 10 minutes. All other ingredients except magnesium stearate were added to the blend and thoroughly mixed. The specified quantity of magnesium stearate was added to the mixture and was blended in double cone blender for 1 minute. The tablets were compressed using a single punch tablet punching machine. The compressed tablets were than subjected to sublimation at 50°C for 60 min.

Table 2 Batch formula per tablet using sublimation method

Ingredient (mg)	Formulation code		
	LODT5	LODT6	LODT7
Labetalol	5	5	5
Crospovidone	24	24	24
Saccharin Sodium	6	6	6
Lactose	85	75	65
Camphor	10	20	30
Talc	3	3	3
Magnesium stearate	2	2	2
TOTAL	**135**	**145**	**155**

Precompression evaluation the formulation blends

All the prepared blends (LODT1-7) were subjected to determination of the micromeritic properties.

Angle of Repose (Jain and Naruka, 2009)

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). Angle of repose (θ) was then calculated by measuring the height and radius (r) of the heap of powder formed using the following formula

$$\tan\theta = \frac{h}{r}$$

Bulk and Tapped Density (Prameela et al., 2010)

A weighed quantity of blend (10g) was taken into a graduated cylinder (50 mL) and measuring the volume of this weight. The bulk density (ϱ bulk) was calculated by the formula

ϱ bulk = weight of the powder/initial volume

The above cylinder containing the powder blend was tapped until no further volume change occurs. The tapped density (ϱ tap) was calculated by the formula

ϱ tap = weight of the powder/finial volume

Hausner's ratio and Carr's Index (Prameela et al., 2010)

Hausner's ratio is the ratio of tapped density to bulk density and is calculated by the following formula

HR = ϱ tap/ ϱ bulk

The Compressibility index is also known as Carr's Index and is calculated using the values of bulk and tapped density using the formula

$$\text{Carrs Index} = \frac{\varrho\,\text{tap} - \varrho\,\text{bulk}}{\varrho\,\text{tap}} \text{ X } 100$$

Evaluation of MDTs (Narmada et al., 2009)

The MDTs prepared using both the methods were subjected to evaluation of the post compression parameters (tablet evaluation) according to guidelines.

Hardness test

The hardness of the formulated tablets was tested using Monsanto type hardness tester. Three tablets from each batch of formulation were randomly taken and the force required to break the tablets was measured using hardness tester.

Friability test

The friability test of the formulations was performed using a Roche type friability test apparatus. Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by the formula

$$\%\,\text{Friability} = \frac{W_{initial} - W_{final}}{W_{initial}} \text{X } 100$$

Weight variation test

20 tablets were randomly taken and weighed to calculate the average weight of the tablets. Each of

these tablets was individually weighed and the difference from average weight was calculated. The percent weight variation was calculated to determine the deviation from the average weight.

Thickness

The thickness of randomly selected tablets from each batch of formulation was measured using a digital vernier caliper.

Drug content

Five tablets from each formulation were weighed to determine the average weight. These tablets were crushed in a mortar then the amount of powder equivalent to 20 mg of drug was dissolved in 5 mL of methanol and the volume was made up to 20 mL using phosphate buffer pH 6.8. 10ml from this stock solution was withdrawn and diluted up to 100 mL with phosphate buffer pH 6.8. 0.6 mL from this stock solution was pipetted out and diluted to 10 mL using phosphate buffer pH 6.8. Absorbance of the resulting solution was measured at 285 nm using UV spectrophotometer.

Wetting time

A piece of tissue paper folded twice was placed in a small petri dish (i.d. = 6.5 cm) containing 10 mL of water, a tablet was placed on the paper, and the time for complete wetting was measured.

Water Absorption ratio

A piece of tissue paper was folded twice and placed in a Petri dish containing 6 mL of 0.5% v/v amaranth solution (as a coloring agent) in water. A tablet was placed gently on the tissue paper, and the wetted tablet was reweighed. The water absorption ratio R was determined according the following equation

$$R = \frac{W_a - W_b}{W_b} \text{ X } 100$$

Where W_a is the weight of tablet after water absorption and W_b is the weight of tablet before water absorption.

In vitro disintegration time

The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. One tablet was placed in each of the 6 tubes of the basket and a perforated disc was placed over each tablet. The assembly was raised and lowered at 30 cycles per minute in the pH 6.8 buffer maintained at 37±2°C. The time required for complete disintegration of the tablet with no palpable mass remaining in the apparatus was recorded.

In-vitro dissolution

The USP type II paddle apparatus with a paddle speed of 50 rpm was used for dissolution testing for the formulated MDTs. The dissolution media used consisted of 900 mL of 0.1 N HCl and distilled water. 5 mL of samples were collected at time points of 5, 10, 15, and 30 min and the media was replenished with the same volume of fresh media. The free drug concentration was estimated using a UV spectrophotometer at a wavelength of 285 nm.

Short term stability study

The formulated MDTs were randomly selected and subjected to three month stability study at 25°C/ 60% and 40°C /75 % RH. After the end of the study period, some critical parameters were evaluated.

Results and Discussion

Preformulation Studies

The physical characterization of the drug obtained revealed that Labetalol is a white colored powder with a bitter taste and melting point of 188-192°C. The drug was freely soluble in water, soluble in methanol, insoluble in chloroform and acetone.

The λmax was found to be 285 nm and used for determination of the drug in solution. The absorbance of 5 to 25 µg/mL solutions was measured at 285 nm by UV spectrophotometer. The linear regression correlation was found to be 0.997 for the calibration curve in phosphate buffer (Figure 1).

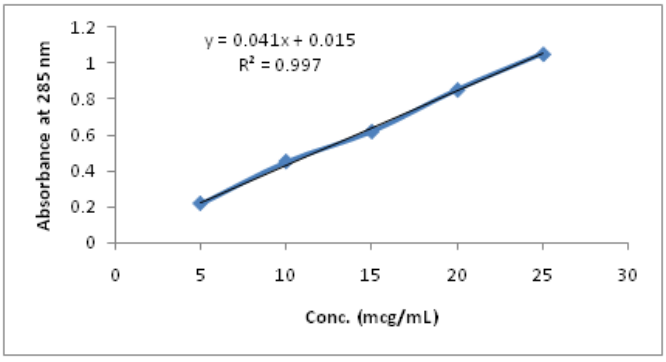

Figure 1 Calibration curve of labetalol in phosphate buffer pH 6.8

Precompression Parameters of the formulation blends

All the formulations were subjected to preformulation testing of the blends in order to ascertain their suitability for compression. The bulk and tapped density, angle of repose, Hausner's ratio and Carr's Index are used to determine the compressibility and flow properties of the blends. The angle of repose is a measure of the frictional forces in the loose powder blend that may hinder the flow property of the blend making it unsuitable for feeding through the hopper of the tablet machine. The angle of repose of all the formulation blends ranged from 29°17' to 30°31'. A θ value of less than 30° of powder or blends is known to exhibit excellent flow properties (Amrutkar et al., 2010).

The results of precompression evaluation of the formulation blends are presented in Table 3. From the results it is evident that all the blends possessed the capability to flow freely and may present no hindrance in compression or tabletting process. The values of Hausner's ratio and Carr's Index are found to be within the specifications of good flow property of powders (Kakade et al., 2010).

Table 3 Precompression parameters of blends

Formulation Code	Bulk density (g/cm^3)	Tap density (g/cm^3)	Angle of repose (°)	Carr's Index (%)	Hausner's Ratio
LODT1	0.391	0.415	29°89'	5.78	1.06
LODT 2	0.384	0.428	30°03'	10.28	1.11
LODT 3	0.397	0.433	30°01'	8.31	1.09

LODT 4	0.376	0.441	30°31'	14.74	1.17
LODT5	0.379	0.429	29°36'	11.66	1.13
LODT 6	0.381	0.437	29°17'	12.81	1.15
LODT 7	0.388	0.443	30°18'	12.42	1.14

Evaluation of MDTs

The hardness of all the tablet formulations was less than 3 Kg/cm^2 indicating uniform hardness and sufficient mechanical strength. The thickness of all the tablets was found to be less than 5 mm and uniform. The weight variation for all the formulations was found to be in the range of ±7.5% specified by the pharmacopoeias for tablets of average weight less than 324 mg. All the formulations exhibited friability of less than 1 % indicating good mechanical strength in the tablets. The drug content of each formulation was determined by using the method described in section 4.6.5 and it was found that all the formulations contained drug content in the range of 97.2 to 98.9 %.

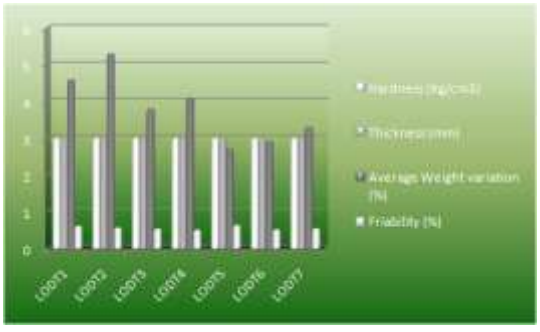

Figure 2 Comparison of Post compression parameters of MDT formulations

It can be easily visualized from the pictorial representation that while thickness and hardness of all the formulations was similar, the average weight variation and friability were lower in sublimed formulations.

The wetting time and water absorption ratio are the indicator of the efficiency of the superdisintegrants. They exhibit the capacity of the disintegrants to absorb water and wet the tablet completely within the shortest time duration. The quick wetting and high water absorption ratio help in swelling of the MDTs and its rapid disintegration and dissolution in the oral cavity. The wetting time of the formulations ranged from 17 to 49 seconds with water absorption ratio of more than 75 % for the formulations (Table 5.5). The results reveal that all the formulations possessed the ability to quickly disintegrate and dissolve (Rampure et al., 2010).

The disintegration time is the minimum time that is needed by the tablets of break down in to smaller particles. The disintegration of the tablets reduces the particles size and in turn increases the total surface area that is available for dissolution of the particles in the site of disintegration. A quick disintegration implies that the drug will be absorbed quickly from the site of disintegration and dissolution thereby producing quick onset of action of the drug. It has been already discussed that the prescribed limit of disintegration for MDTs is 30 seconds and in certain cases for fast dissolving tablets it can be up to 3 minutes. All the formulations exhibited of less than

30 seconds in the *in vitro* test ranging from 16.4 to 29.3 seconds

All the formulations were found to release more than 80 % of the drug within a period of 5 minutes (Table 4). While LODT1 exhibited the lowest release of drug (81.2 %), the highest amount of drug was released from LODT6 (97.1 %).

The release rate was found to be higher in the formulations prepared by sublimation method as compared to those formulated by direct compression method. The higher porosity formed in the tablets during the sublimation process may be responsible for quicker disintegration and higher release of drug from the formulations.

Table 4 Wetting, water absorption, disintegration and drug release of MDTs

Formulation Code	Wetting time (seconds)	Water absorption ratio	Disintegration time (seconds)	Drug release (%)
LODT1	49	76.8	27.2	81.20
LODT2	41	82.2	29.3	89.70
LODT3	37	75.9	[illegible]	[illegible]
LODT4	24	87.4	[illegible]	[illegible]
LODT5	21	77.5	21.5	96.50
LODT6	17	88.6	[illegible]	[illegible]
LODT7	28	89.1	[illegible]	[illegible]

The tablets prepared by direct compression method exhibited relatively poor dissolving capabilities compared to those prepared by sublimation method. Sodium starch glycolate containing tablets usually present high capillary activity and pronounce hydration and oppose gelling thereby causing rapid disintegration and drug release. On the other hand tablets prepared by sublimation method have the lowest hardness and their porous structure is responsible for rapid water uptake, thereby facilitating the wicking action of methyl cellulose in bringing about faster disintegration (Prakash et al., 2008).

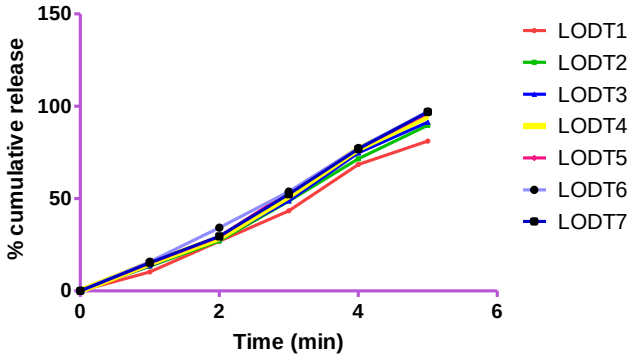

Figure 3 *In vitro* drug release from formulations

Accelerated stability testing was performed on 15 tablets of all formulations by storing them in amber colored stoppered vials at specified conditions of temperature and humidity for a period of 3 months. At intervals of one month, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time. A very small change in disintegration time, drug content and friability was observed in almost all the formulations under the conditions of the study.

Conclusion

It can be concluded from the study that mouth dissolving tablets of labetalol could be easily formulated using super-disintegrants and sublimating agents in order to achieve a rapid onset of drug action and peak plasma concentration over short period of time. The MDTs formulated using could be highly beneficial for the management of hypertensive crisis that require immediate attention and lowering of blood pressure.

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